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WO 97/34565 A1 DE 019603788 A1 FR 002614791 A1
Plant. Med. Phytother. Vol 12, No 3, 1978; M
Haag-Berrurier, pages 197-206 & CAS Abstract No
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(54) Abstract Title

A method of producing high anti-inflammatory activity extracts from harpagophytum procumbens

(57) Extraction of the root of Harpagophytum procumbens with liquid carbon dioxide in the presence of a co-solvent gives a much higher yield of harpagoside, an iridoid glycoside with anti-inflammatory properties, in the extract in comparison to the known aqueous or aqueous-alcoholic extraction methods. An extract containing 10% of harpagoside by weight of extract (which corresponds to a yield of 1.5% by weight of starting harpagophytum root material placed in the separator) was obtained when 10% ethanol was used as co-solvent, in conjunction with super-critical carbon dioxide (4000 psi/41°C). Tablets containing this extract were produced using a direct compression method. An enteric coating was then applied to the tablets by dissolving a coating solution of cellulose acetate phthalate (10% by weight) in iso-propanol/acetone in a heated rotary coating pan. The tablets thus obtained contain harpagophytum extract equivalent to 1g of whole herb.

The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1995

This print takes account of replacement documents submitted after the date of filing to enable the application to comply with the formal requirements of the Patents Rules 1995

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A METHOD FOR PRODUCING HIGH ACTIVITY EXTRACTS FROM
HARPAGOPHYTUM PROCUMBENS

This invention relates to a novel extract from the root of Harpagophytum procumbens (Devil's Claw) that contains high levels of the compound harpagoside. Harpagoside exhibits anti-inflammatory and analgesic activity in standard animal modes. The invention also relates to a method of producing such an extract.

Preparations derived from the root of Harpagophytum procumbens (also known as Devils Claw) have traditionally been used in the symptomatic treatment of chronic inflammatory diseases such as rheumatism and arthritis. The widespread use of preparations of devils claw and their generally accepted efficacy and safety has been recognised by the introduction of an official monograph into both the 3rd Edition of the European Pharmacopoeia and the current British Pharmacopocia. Extracts derived from harpagophytum have been demonstrated to exhibit significant anti-inflammatory activity and analgesic activity in a range of standard *in vivo* animal models (M C Lanhers et al, Planta Medica, 58 117-123 (1992)). The above pharmacological activity was much more pronounced in chronic models rather than short term acute studies (R Grahame & B V Robinson, Ann Rheum Dis, 40, 632 (1981)).

In several of the studies, samples of pure harpagoside (an iridoid glycoside isolated from harpagophytum root) (F C Czygan & A Kruger, Planta Med, 31 305-307 (1997)) also ^{crude} exhibited comparable pharmacological activity to that observed for the crude harpagophytum extracts indicating that this is probably the active constituent (O Eichler & C Koch Arnzhelm Forsch, 20, 107-109 (1970)). These experimental indications of efficacy have been largely confirmed by several clinical trials which revealed statistically significant improvements in the symptoms of rheumatic disease

for harpagophytum extracts usually standardised on harpagoside content (S C Chrubasik, Phytomedicine, 3 (1), 1-10 (1997) and P Belaiche, Phytotherapy, 1, 22-28 (1982)).

The central importance of harpagoside in ensuring the efficacy of harpagophytum preparations is emphasised by the European Pharmacopoeia monograph stipulating a minimum harpagoside content of 1.2% W/W for harpagophytum root which is to be used medicinally (European Pharmacopoeia, 3rd Edition, P716-717 (1997)).

In addition, to the harpagoside and other related iridoid glycosides, the root of harpagophytum contains large quantities of simple sugars such as stachyose and sucrose ("British Herbal Compendium", Vol 1, Ed P R Bradley, BHMA (1992) (p78-82)). This has the result of producing very large extractive values of up to 70% (70g of extract from 100g raw herb) when aqueous or aqueous-alcoholic extraction is employed.

This is reflected in the specification of the best commercially available extracts which have an extractive value of around 40% and harpagoside content of only approximately 2.1% W/W approximately.

The large mass of extract produced per gramme of herb is unsatisfactory as this has the effect of diluting the concentration of the extracted harpagoside, resulting in unrealistically high dose of extract being required to administer an effective dose of harpagoside. The large number of tablets that this corresponds to has unfavourable implications for patient compliance and hence efficacy.

A further problem associated with the medicinal use of harpagophytum extracts is the sensitivity of the active components to degradation by stomach acid. Thus, a study comparing the effect of the route of administration of harpagophytum extract on the anti-inflammatory action in test animals demonstrated the same extract to be very active by intraperitoneal injection by completely ineffective when

given orally (M C Lanhers et al, Planta Medica, 58 117-123 (1992)).

An *in vitro* study produced similar results showing loss of previously demonstrated anti-inflammatory activity after an extract had been treated with 0.1M hydrochloric acid (R Soulimani et al, Can J Physiol Pharmacol, 72, 1532-1536 (1992)).

In recent years, extraction using liquified carbon dioxide has been applied to production of fractions rich in biologically active compounds from plant based raw materials (European Patent EP58365; European Patent EP553658; and D A Moyler, Flav & Frag J, 8 235-247 (1993)).

Liquid carbon dioxide has a high selectivity, being able to solubilise low molar mass compounds of moderate polarity whilst leaving behind in the matrix higher molecular weight lipids, waxes and pigments which would otherwise increase the bulk of an extract and dilute the actives content (G Wilke Angew, Chem Int Eng Ed 17, 710 (1978)). Liquid carbon dioxide is also superior to non-polar organic solvents in that it is non-flammable, so that the solvent can be safely vented to the atmosphere avoiding waste disposal and recycling costs. The intrinsically non-toxic and highly volatile nature of carbon dioxide avoids any problems of elimination of residual levels of harmful solvents from the product.

According to a first aspect the present invention provides a method of preparation of an extract containing harpagoside comprising the step of extracting harpagophytum root with liquid carbon dioxide and allowing the carbon dioxide to evaporate from the resultant mixture

According to a second aspect of the invention there is provided an extract from harpagophytum root containing an amount of more than 3%, preferably more than 5%, particularly preferably more than 7%, especially preferably more than 9%

by weight of harpagoside, the extract not containing any residual solvent.

The resultant residual extract contains a higher percentage of harpagoside than may be obtained by solvent extraction using aqueous alcoholic mixtures.

A co-solvent may be employed in the method of the invention for example a polar hydroxylic solvent such as a C₁₋₄-alcohol, preferably ethanol. The co-solvent is preferably present in an amount in the range 1-20%, preferably 5-15%, particularly preferably about 10% by weight. Preferred methods of the invention employ a co-solvent as this has been found to give proportions of harpagoside typically greater than 9%.

Preferred methods of extraction are carried out at a pressure in the range 1400-5000psi (96 to 343bar), particularly preferably at about 4000psi (276bar).

Use of a pressure of 1400 to 4000psi, preferably 1400 to 1500psi at a temperature of 20-45°C is preferred.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising an extract according to the invention together with one or more physiologically acceptable carriers or excipients. Preferably, the composition is orally administrable and for this purpose is preferably provided with an enteric coating (e.g. cellulose acetate phthalate).

The invention is further described by means of example by not in any limitative sense.

Example

Roughly ground root of *Harpagophytum procumbens* was packed into a suitable pressured vessel. A volume of liquid carbon dioxide at the ratio approximately 10ml of liquid carbon dioxide per 1g of herb was allowed to pass through the raw material at a flow rate of approximately 2ml/min. The

liquid carbon dioxide was then collected, the pressure released and carbon dioxide allowed to vent to the atmosphere. Removal of any added co-solvent or residual moisture was completed by drying in a vacuum desiccator. The residual extract in the collection vessel was an oil or semi-solid depending on the exact extraction conditions.

The following range of extraction conditions were employed:

SAMPLE	PRESSURE	TEMP	CO-SOLVENT	% YIELD	% W/W HARPAGOSIDE
DC1	1500	27°C	NONE	0.4%	0%
DC2	1500	27°C	1%	0.8%	0.03%
DC3	4000	41°C	NONE	0.4%	0%
DC4	4000	41°C	1%	0.4%	1.6%
DC5	4000	41°C	10%	1.5%	10.0%

The harpagoside content was determined by an HPLC method based on that described in the monograph for Devils Claw (*Harpagophytum*) in the Third Edition of the European Pharmacopoeia.

The harpagoside content of the harpagophytum root starting material was determined to 0.9% by the same European Pharmacopoeia method.

Sub-critical liquid CO₂ (25°C/1500psi) liquid CO₂ close to the critical temp (36°C/1440psi) and supercritical CO₂ significantly above the critical temperature (36°C/4000psi) gave products containing limited proportions of harpagoside.

The addition of 10% ethanol co-solvent has been found to significantly increase the content of harpagoside compared to the use of pure liquid carbon dioxide.

The use of supercritical carbon dioxide combined with 10% ethanol co-solvent yields the maximum concentration of harpagoside in the extract and thus represents the preferred embodiment of the invention.

For the purposes of producing tables the extract is dissolved in the minimum quantity of ethanol and absorbed on to an inert pharmaceutical excipient, preferably Maltodextrin, and the solvent allowed to evaporate at room temperature. In the preferred embodiment of the invention 15g of extract is absorbed per 100g of Maltodextrin.

The extract adsorbate may then be mixed with pharmaceutical excipients and compressed into tablets using a rotary tablet press.

The following direct compression formulation represents a suitable example of a tablet mixture:

100mg	Harpagophytum extract adsorbate
194mg	Direct Compression Lactose
50mg	Microcrystalline Cellulose
50mg	Pre-gelatinised Starch
2mg	Magnesium Stearate
2mg	Stearic acid
<u>2mg</u>	Amorphous Silica
400mg	

The tablets are then coated with a suitable enteric coating solution. In the preferred embodiment of the invention a solution of cellulose acetate phthalate is employed, to protect them from degradation by stomach acid. Typically, 10% by weight of cellulose acetate phthalate is applied to the tablet cores as a solution in acetone/isopropanol in a heated rotary coating pan.

This produces a table containing harpagophytum extract equivalent to 1g of whole herb.

CLAIMS:

1. A method for preparing an extract containing harpagoside comprising the steps of extracting harpagophytum root with liquid carbon dioxide and allowing the carbon dioxide to evaporate from the resultant mixture.
2. A method as claimed in claim 1 carried out in the presence of a co-solvent.
3. A method as claimed in claim 2 in which the co-solvent is a polar hydroxylic solvent.
4. A method as claimed in claim 2 or 3, in which the co-solvent is a C₁₋₄-alcohol.
5. A method as claimed in claim 2, 3 or 4 in which the alcohol is ethanol.
6. A method as claimed in any preceding claim using sub-critical or super-critical liquid carbon dioxide.
7. A method as claimed in any preceding claim using super-critical carbon dioxide.
8. An extract from harpagophytum root comprising more than 3wt% of harpagoside.
9. An extract as claimed in claim 8 comprising more than 5wt% harpagoside.
10. An extract as claimed in claim 8 or claim 9 comprising more than 7wt% harpagoside.

11. An extract as claimed in any of claims 8 to 10 comprising more than 9wt% of harpagoside.

12. A pharmaceutical composition comprising an extract as defined in any of claims 8 to 11 together with one or more physiologically acceptable carriers or excipients.

13. A method for combatting inflammatory conditions in a subject comprising administering to said subject an effective amount of an extract as defined in any of claims 8 to 11 or of a pharmaceutical composition as defined in claim 12.

14. Use of an extract as defined in any of claims 8 to 11 for the manufacture of a medicament for use in combatting inflammatory conditions.

15. A method for preparing an extract containing harpagoside as hereinbefore described in the examples.

16. An extract from harpagophytum root as hereinbefore described in the examples.



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Claims searched: 1-16

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Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK CI (Ed.Q):

Int CI (Ed.6):

Other: Online: CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
A	DE 19603788 A1 (CHRUBASIK), see page 1, lines 46-47; and CAS Online Abstract No. 127:166771	-
X	FR 2614791 A1 (MOATI), see especially page 3, paras 5 & 6; and CAS Online Abstract No. 111:180743	8, 12-14
X	WO 97/34565 A1 (STUMPF et al.), see Beispeil 2, 3, 5 & 6; page 2, para 4; see also WPI Abstract Accession No. 97-479962 [44] and CAS Online Abstract No. 127:268011.	8-14
A	Plant. Med. Phytother. Vol 12, No 3, 1978; M Haag-Berrurier, pages 197-206, see especially "Resultats", pages 203-204; see also CAS Online Abstract No. 90: 76624.	-

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.